

The viral envelope in the evolution of HIV: a hypothetical approach to inducing an effective immune response to the virus

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Abstract — The human immunodeficiency virus (HIV) is 'perceived' by the host immune system as *partly-self* because of the presence of host cell wall membrane on the viral envelope. This perception leads to an ineffective immune response to the virus. It is proposed that only viral core antigens without the envelope will be perceived as *non-self* by the host immune system and can provoke an effective immune response. In normal uninfected persons, core antigens could therefore serve as a vaccine. In HIV infected persons, uncommitted immunocytes from the peripheral leucocytes freed from antibodies will in vitro process autologous viral core antigens as *non-self antigens* and lead to an effective immune response against the HIV when reinjected into the patient. The use of autologous viral core antigens provides, at the same time, a means for testing viral core antigens as possible vaccines without any risk to a third person. This immunotherapy of the HIV, when confirmed, will support core antigens as possible vaccines and could also be applied to the large group of retroviral and other enveloped viruses that cause chronic infections and malignant tumours in man and animals, with considerable benefits to human and animal health.

Introduction

The human immunodeficiency virus (HIV) (1) is unquestionably one of the most widely studied viruses in medical history, especially its genetics and molecular biology. Yet, prospects for an effective treatment or a vaccine for the virus are still remote. It is of fundamental importance to the immunology of the virus and to vaccines to first understand why the immune responses of the body to the virus fail to eliminate it. The long survival

of some HIV seropositive patients (2) has not really contributed to this understanding. Current opinion attributes the failure of immune response to eliminate the virus to the genomic heterogeneity and the continuing mutations of the virus in different patients (3) and even within the same patient (4) which has enabled the virus to escape from the host immune responses (5). Its genetic diversity and capacity for mutation constitute, in the opinion of experts (6), major obstacles to the development of an effective treatment and vaccine for the virus.

This paper re-examines a different explanation that had been previously proposed (7) for the failure of the immune responses to eliminate the virus from the body and proposes a hypothetical approach to inducing an effective immune response to the virus which could provide the basis for the immunotherapy of infected persons and the production of a vaccine to the HIV.

A crucial mutation of the HIV

The HIV has indeed an undisputed genetic diversity and capacity for mutations. Viral mutations which adapt the virus to survive better in its host are likely to be perpetuated. The HIV is an enveloped virus, and given the existence of other non-enveloped viruses, it must have acquired its envelope from the host cell in an earlier mutation which allowed the pre-envelope ancestor of the HIV to improve its survival in the body. As will be seen in the following two sections, the viral envelope has indeed contributed to the survival of the HIV in the body, partly by participating in, and facilitating, the infection of other host cells by the virus but mainly by modifying the host immune response in its own favour which has given the HIV a secure foothold in the body. Without this secure foothold and protection from the host immune system achieved with the help of the viral envelope, the HIV would be easily eliminated from the body and so the genetic diversity and mutations now observed in the virus might well not have occurred.

The envelope of the HIV

The viral envelope, as is well known, consists of a membrane of cellular origin on which viral surface antigens are attached. It plays a crucial role in the life of the virus (8). Only enveloped viral particles can normally infect other cells, and fusion of the viral envelope membrane to the target host cell membrane to be infected, initiated by the action of GP120 and GP41 on the CD4 receptor, precedes and facilitates the infection of that cell (9). The viral envelope is derived by budding from the host cell wall as the virus leaves the cell after multiplication. In carrying host cell wall membrane in its envelope, the virus is, for that reason, perceived by the host immune system as partly-self. This perception does not change with the mutations that may occur in the core and surface antigens of the virus, because the viral envelope membrane is always of host origin.

Thus, in addition to serving as a scaffold for surface antigens and for facilitating the infection of new host

cells by the virus, the viral envelope presents the virus to the host immune system as partly-self. This last function has important consequences on the patient's immune system.

The viral envelope and the host immune system

The host immune response to a virus that is perceived as partly-self is bound to be less effective than that to a virus that is perceived as completely non-self. If the host immune system were indeed to ignore the presence of its cell membrane on the virus and so consider the virus as completely non-self, it should, immunologically, effectively destroy the virus and, with it, those host cells (CD4⁺) from which the viral envelope was derived because the CD4⁺ cells carry the same antigens present on the viral envelope. This host cell destruction would constitute a serious auto-immune disease (10) which, if permitted, can only aggravate and accelerate the destruction of the host immune system. Infections with HIV would then lead rapidly to AIDS and to death in the few weeks or months that it takes for the host immune system to respond. In that period, the patient would be rid of his virus but would then die from a new acquired auto-immune deficiency syndrome, AAIDS. Clinical experience shows that in a few persons, the course of the HIV infection is so short and fulminant as to suggest that AAIDS might indeed have occurred. Such persons often have severe thrombocytopenia with haemorrhages, severe leucopenia and severe anaemia despite the transfusion of large volumes of blood, and they frequently die in a matter of months from the onset of the infection.

In the vast majority of persons, however, the natural history of HIV infections is relatively long (the HIV belongs to the lentiviruses (11)) and suggests, therefore, that the auto-immune catastrophe described above does not occur, because the host immune system, recognizing its own cell membrane elements in the viral envelope and considering the virus as partly-self, is obliged to avoid its auto-destruction by compromise, by producing an immune response that does not destroy the virus in order not to destroy itself with the virus. The HIV would thus appear to have succeeded in using its envelope, obtained from host cells, in a kind of 'blackmail', to prevent the production of an immune response that is effective against itself. It is a 'blackmail' that is simple, effective, achieved from the start of the infection and lasts throughout the infection, leaving no trace that would call attention to the blackmailing envelope. The so-called envelope antibodies are antibodies to antigens GP120/GP41 attached to the viral

envelope but not to itself. Of the antibodies to the HIV, the antibodies to the viral envelope, and not to the core, are the most important in the immune response. The viral envelope, and not the core, is the presence of the viral envelope that makes the virus dangerous to the host.

The hypothesis

In the light of the above, it is proposed that only the viral envelope, and not the core, can, from the host immune response in the body, have important consequences on the patient's immune system.

1. When a virus is injected into the body, the host immune system, recognizing the viral envelope as partly-self, produces an effective immune response against the virus, but this response is ineffective against the core, and the virus is not destroyed. (This is the subject of the associated discussion.)
2. The HIV virus, with its P20, GP120, GP41, and its core antigen, is a cytotoxic virus. The core antigen, being a core antigen, is not recognized from the host immune system, and the action of the virus is through its core antigen, and not through its envelope.

The peripheral immune system, especially the lymphocytes, is committed to the process of destruction and invasion of the body, and such uncommonly, an effective immune response is normally produced by the synthesis of antibodies in the body, by the host immune system, and in a suitably timed manner to the HIV, so that the core is perceived as core.

envelope but not to the viral envelope membrane itself. Of the capacities for mutation that characterize the HIV, the one by which the virus first acquired an envelope, as stated above, was clearly the most important since, in preventing an effective host immune response, it assured its survival in the body. The viral envelope is indeed the secret weapon of the HIV, and 'blackmail' is its modus operandi. It is the presence of host cell wall membrane as part of the viral envelope that makes the HIV such a dangerous virus!

The hypothesis

In the light of the foregoing, the hypothesis proposes that only viral core antigens alone, without an envelope, can, from the start, provoke an effective immune response in the body against the HIV. This hypothesis has important implications for (a) normal uninfected persons and (b) for HIV infected persons.

1. When viral core antigens without viral envelopes are injected into the normal person uninfected with HIV, they will be perceived by the person's immune system as non-self and should provoke an effective immune response which can protect against the HIV and could therefore serve as a vaccine. (The difficulties, problems and fears associated with this proposal are examined in the discussion.)
2. The HIV infected person has antibodies to P18, P20, GP120/41, and cell mediated responses or cytotoxic T-lymphocytes (12) directed at the viral core antigens, but these fail to eliminate the virus from the body, as suggested above, because of the action of blackmail which the viral envelope, through its antibodies, exercises over the entire host immune system from the start of the infection.

The peripheral leucocytes of HIV infected persons, especially seropositives in category A of the new classification of AIDS (1993), contain macrophages, lymphocytes and other immunocytes which are uncommitted to the HIV and are therefore free to process and deal with other or new antigens that may invade the body. In the infected person, however, such uncommitted immunocytes are prevented from an effective immune response to core antigens that are normally produced in vivo in defective viral synthesis or even those introduced directly into the body, by the prior action of the viral envelope on the immune system of the patient. In vitro, however, and in a suitable culture medium free from antibodies to the HIV, such uncommitted immunocytes would perceive core antigens of HIV without the envelope

as new non-self antigens, and would process them accordingly. Thus, when autologous viral core antigens (AVCA) are cultured for a while with the corresponding uncommitted immunocytes in a medium free from HIV antibodies and then reinjected into the infected person concerned, a new subset of immunocytes sensitized in vitro to viral core antigens alone, will carry the immune process to term in vivo from which an effective immune response will progressively eliminate only the viral cores of the virus. This new effective response will, for a while, co-exist with the old ineffective immune responses started in the body under the blackmail of the viral envelope, but will eventually supersede them.

In practice, autologous viral core antigens (AVCA) would be prepared in vitro, from a sample of the patient's blood which contains enveloped viruses, by treating it with chloroform or ether which destroys the viral envelope by virtue of its lipoprotein content. (The details of this process remain to be worked out.) After removing the chloroform or ether, the AVCA would be cultured in vitro with the patient's peripheral leucocytes in a suitable culture medium free of HIV antibodies as described above, before being reinjected into the patient.

For success of the above procedure, it is important that there be an adequate number of uncommitted immunocytes in the peripheral leucocytes of the seropositive person. Clinical symptoms or signs of AIDS, especially the presence of opportunistic infections, is already evidence that any uncommitted immunocytes will have been mostly used up; this should exclude such patients from this procedure. The AVCA must also be prepared correctly, removing completely only the viral envelope of all viruses without destroying the core antigens. (Electron microscopy could be used to verify that the envelope is removed completely and the AVCA could be checked for the presence of the HIV RNA using standard laboratory methods.) The in vitro culturing should be long enough for the immunocytes to be sensitized with the AVCA before being reinjected into the person.

The above procedure should be repeated at suitable intervals using fresh leucocytes and AVCA to re-inforce the immune response and to forestall the emergence of new mutants of the virus.

Discussion

The evolution of the HIV is of the greatest importance to the understanding of the behaviour of the virus as it now presents in the body. The ancestor of the present virus had no envelope and caused an infection that was probably not chronic. The mutation(s) by

which the virus finally acquired its envelope from its host was an event of the greatest importance to the virus because it enabled the virus to survive and cause a chronic infection in the body by blackmailing the host immune system into an ineffective response.

Recognizing the importance of the envelope and wishing, so to speak, to return the HIV to its pre-envelope period, the hypothesis proposes stopping the virus by depriving it of its blackmailing envelope. When viral core antigens, without the envelope, are injected into uninfected persons, they will be perceived by the immune system as non-self antigens and accordingly provoke an effective immune response directed exclusively at the viral cores. The problem then would be to explain how this response restricted to core antigens alone can destroy the whole virus and so serve as a vaccine when the sensitized person is later infected by the enveloped HIV.

The effective immune response to core antigens will include, as for other non-self antigens, both antibodies which are too large to penetrate the viral envelope, and a cell-mediated response, with cytotoxic lymphocytes (CTLs), which can destroy core antigens within the viral envelope of an infecting virus. With such destruction, core antigens alone could therefore serve as an effective vaccine for the HIV virus concerned. Using several types and sub-groups of the HIV, one could, in theory, prepare appropriate vaccines which, to avoid immune paralysis, could be administered individually at suitable intervals over a period.

Core antigens are unlikely to be accepted at present as vaccines in humans before their long-term effects are known. The viral core without its envelope can, after all, be considered as a kind of 'prehistoric virus' before it became the HIV by acquiring an envelope. As viruses then, they could, in theory, cause infections, although in practice the viral cores alone have now lost the capacity to infect - only enveloped viruses can now normally infect other cells. Therefore, if it could be shown that autologous viral core antigens (AVCAs) could indeed provoke an effective immune response in HIV sero-positives without any untoward long-term consequences, this would further strengthen the case for core antigens as possible agents for vaccines.

Based on the presence of uncommitted immunocytes in the peripheral leucocytes of HIV sero-positives, it is claimed that such immunocytes, when sensitized *in vitro* in a medium free of HIV antibodies, should start to process AVCA as non-self antigens, and when reinjected into the person, will lead, at term, to an effective immune response *in vivo*.

As regards their innocuity, the AVCA prepared from the seropositive cannot reinfect the person *in*

vivo, and without their envelope they cannot infect the immunocytes *in vitro* either, which, in the circumstances, must process the AVCA as simple non-self antigens - and lead, *in vivo*, to an effective immune response which will eliminate only core antigens within the viral envelope as explained above. That response should also eliminate the viral genome present or dormant in any host cells, but similar uninfected cells and the viral envelopes will not be affected. Following the start of this response, the internal reinfection of host cells by the virus will progressively stop and the virus itself will be eventually eliminated from the body. In time, levels of the usual HIV antibodies will fall and perhaps disappear after some years. The PCR could then be used to confirm the complete elimination of the virus from the body.

The positive outcome predicted for the use of AVCA as described above constitutes a method for the immunotherapy of the HIV which should also serve as a kind of vaccine and prevent reinfection in the person concerned. The use of AVCA provides, at the same time, a means for testing viral core antigens as possible vaccines without any risk to a third person. Whilst it would be difficult, for logistic reasons, to treat all the seropositives that could benefit from it, positive results obtained in an adequate sample would provide the additional evidence that confirms the claims of this hypothesis. Such evidence should at least redirect and focus further research attention on the core of the virus.

It should be noted that in proposing the use of AVCA for the immunotherapy of the HIV, one is in fact proposing the use of parts of the infecting virus to treat the infection by the same virus - 'setting a thief to catch a thief' (7) or 'paying the virus in its own money'. This form of immunotherapy, when confirmed, could be applied to other retroviral infections of man such as the human T-cell leukaemia virus, HTLV-1 (13), and animals (14-16) and even to other enveloped viruses such as the EBV and the cytomegalovirus (CMV) (17,18) which cause chronic infections and malignant tumours in AIDS and other groups of patients. The benefit to human and animal health would be considerable. The hypothesis, when confirmed, would then have contributed to finding a vaccine and treatment for the HIV.

Summary

The HIV carries host cell wall membrane as part of its envelope and is therefore perceived by host immune system as *partly-self*. This perception blackmails the host immune system into a response that does

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not destroy the virus in order not to destroy itself with the virus. The viral envelope therefore helps the HIV to prevent an effective immune response in the host to itself. The hypothesis proposes that only core antigens without the envelope will be perceived as *non-self antigens* by the host immune system and provoke an effective response. In a normal uninfected person, this effective immune response to the core antigens alone can serve as an effective vaccine for the HIV. In persons already infected with the HIV, however, autologous viral core antigens (AVCA), prepared from their own blood will not provoke an effective immune response *in vivo* because of the blocking antibodies produced in the body under the influence of the viral envelope. Uncommitted immunocytes from their peripheral leucocytes, however, when freed from all antibodies, can *in vitro* process AVCA as non-self antigens and lead to an effective immune response when the cells sensitized *in vitro* are re-injected into the patient, and this will eventually lead to the total elimination of the virus from the patient. *The use of AVCA provides, at the same time, a means for testing viral core antigens as possible vaccines without any risk to a third party.* This form of immunotherapy can be applied to other retroviral infections in man and animals and even to other chronic infections and malignant tumours caused by other enveloped viruses, with considerable benefits to human and animal health. There is therefore an urgent need to confirm this hypothesis, which could lead to an effective vaccine and treatment of the HIV and other enveloped viruses.

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